This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[HA682 trade name][*]
Manufacturer of Prequalified Product:	Hetero Labs Limited Unit – III (Formulations) # 22 – 110, IDA Jeedimetla, Hyderabad – 500 055 Telangana, India
Active Pharmaceutical Ingredients (APIs):	Dolutegravir sodium
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, other antivirals. (J05AX12)
Therapeutic indication:	[HA682 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40 kg.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

1. Introduction

[HA682 trade name] is indicated is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40 kg.

[HA682 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

2. Assessment of Quality

The assessment was done in accordance with the requirements of *WHO's Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredient (API)

The API is the sodium salt of dolutegravir. It is very slightly hygroscopic and contains 2 stereogenic carbon centres. The API is manufactured as a pure enantiomer: sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1', 2':4,5]pyrazino[2, 1-b][1,3]oxazin-7 –olate. The molecular structure of Dolutegravir sodium was investigated and confirmed by FT IR, UV, NMR, MS and elemental analysis.

Dolutegravir sodium is critically insoluble (of BCS low solubility across the physiological pH range), hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. The API exhibits polymorphism and it has been demonstrated by X-ray powder diffraction (XRPD) that the manufacturing process consistently yields one polymorphic form, called Form I. The acceptance criteria for PSD were set on information of the API lot used in the FPP biobatch.

The API specifications include tests for description, solubility, identification (IR, HPLC), polymorphic form (XRPD), water content, sodium content, related compounds (HPLC), assay (HPLC), residual solvents (GC), palladium content (ICP-MS) and particle size. Since the API is critically insoluble, PSD and XRPD also form part of the retest parameters. The test procedures have been adequately validated.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, povidone, sodium starch glycolate, microcrystalline cellulose and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, macrogol/polyethylene glycol, talc, titanium dioxide, red iron oxide red, yellow iron oxide and black iron oxide. None of the excipients used in the manufacture of the tablets are of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink, round, biconvex, film coated tablet debossed with 'H' on one side and 'D 13' on the other side. The tablets are presented in Alu/Alu blisters and HDPE bottles with child resistant caps.

The development of the proposed formulation of the multisource product was based on the pharmacokinetic properties and physico-chemical characteristics of the WHO recommended comparator product, Tivicay® 50 mg tablets. The selection of the core tablet excipients resulted from information available on the qualitative composition of the comparator product, and supported by API-excipient compatibility studies conducted on binary mixtures.

Dolutegravir exhibits very poor flow properties; hence a high shear wet granulation process was chosen to improve the flow properties of the final blend. The manufacturing process includes dry

mixing of the API with excipients, granulation, drying, sifting, milling, blending, pre-lubrication, lubrication, compression and film-coating.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Trial batches were produced and optimized to meet the pre-set quality standards in-line with the characterization of the WHO recommended comparator product.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), average weight, water content, uniformity of dosage units (by content uniformity), dissolution (HPLC), related compounds (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The results for all parameters at these storage conditions were within agreed acceptance criteria and no negative trend or atypical results were observed. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

An open label, randomized, two treatment, two sequence, two period, single dose, cross over, bioequivalence study of Dolutegravir 50 mg Tablets of Hetero Labs Limited, India and Tivicay® (dolutegravir) 50 mg tablets of ViiV Healthcare Research Triangle Park, NC 27709 in healthy, adult, human subjects under fasting conditions (study no. AZ/BE/05/16/12).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablet manufactured by/for Hetero Labs Limited, India (test drug) with the reference formulation Tivicay® (ViiV Healthcare Research Triangle Park) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Dolutegravir 50 mg (dolutegravir 50 mg) Batch no. E151747.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 5ZP9986.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for dolutegravir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for dolutegravir.

The study was performed with 54 participants; data generated from a total of 53 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dolutegravir as well as statistical results are summarised in the following table:

Dolutegravir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (geometric mean)	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.48 ± 1.21	2.71 ± 1.12	-	-
C_{max} (ng/mL)	3493 ± 1148 (3308)	3131 ± 969 (2987)	110.8	100.7 – 121.8
AUC_{0-72h} (ng·h/mL)	61880 ± 20465 (58720)	57683 ± 18489 (54576)	107.6	98.9 – 117.1
AUC_{0-inf} (ng·h/mL)	65621 ± 21877 (62268)	61851 ± 20280 (58426)	106.6	98.4 – 115.4

The results of the study show that the preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding dolutegravir. Accordingly, the test Dolutegravir 50 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay® (ViiV Healthcare Research Triangle Park).

4. Summary of Product Safety and Efficacy

[HA682 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator product. According to the submitted data on quality and bioavailability [HA682 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into account. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA682 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA682 trade name] has shown to be bioequivalent with Tivicay® (ViiV Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA682 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA682 trade name] was acceptable for the following indication: **" in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg"** and has advised that quality, efficacy and safety of [HA682 trade name] allow inclusion of [HA682 trade name], manufactured at Hetero Labs Limited, Unit – III (Formulations), # 22 – 110, IDA, Jeedimetla, Hyderabad- 500 055, Telangana, India, in the list of prequalified medicinal products.